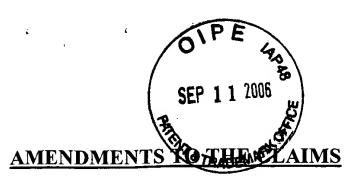
L. SHAPIRO Application No.: 09/518,081



The following listing of claims replaces all prior versions and listing of claims in the application.

1. (Currently Amended) A method of inhibiting apoptosis in a subject, comprising: administering a therapeutically effective amount of at least one serine protease inhibitor in which the effective amount inhibits apoptosis, and monitoring a decrease in apoptosis;

wherein the subject suffers from at least one of Alzheimer's disease, arthritis, muscular dystrophy, Downs Syndrome, multiple sclerosis, arteriosclerosis, autoimmune disease, ischemia-reperfusion injury or neurodegenerative disease, myocardial infarction, or stroke.

- 2. (Canceled) The method of Claim 1 further comprising monitoring a decrease in apoptosis.
- 3. (Previously Amended) The method of Claim 1, in which the serine protease inhibitor is  $\alpha_1$ -antitrypsin, an oxidation-resistant  $\alpha_1$ -antitrypsin Met<sup>358</sup> variant or a free radical-resistant  $\alpha_1$ -antitrypsin Met<sup>358</sup> variants.
- 4. (Previously Presented) The method of Claim 3 in which the effective amount is at least .001 and no greater than 70 g/kg body weight.
- 5. (Withdrawn) The method of Claim 1, in which the serine protease inhibitor is a substituted oxydiazole, thiadiazole, triazole peptoids, or combinations thereof.
- 6. (Withdrawn) The method of Claim 5, in which the serine protease inhibitor is derivatized by esterification, acetylation, or amidation, and wherein the derivatized serine protease inhibitor retains the inhibitory activity.

- 7. (Original) The method of Claim 1, further comprising administering at least one free radical scavenger or inhibitor.
- 8. (Withdrawn) The method of Claim 1, in which the serine protease inhibitor is selected from the group consisting of:
  - i. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
  - ii. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(2-phenylethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
  - iii. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(2-methoxybenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
  - iv. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(trifluoromethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
  - v. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(methyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)- methylpropyl]-L-prolinamide;
  - vi. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(difluoromethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
  - vii. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(benzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
  - viii. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-methoxybenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)- methylpropyl]-L-prolinamide;
  - ix. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(2,6-difluorobenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
  - x. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(trans-styryl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
  - xi. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(trans-4-trifluoromethylstyryl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
  - xii. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(trans-4-methoxystyryl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

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xiii. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-thienylmethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
xiv. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(phenyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
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xv. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-phenylpropyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide.

xvi. (benzyloxycarbonyl)-L-valyl-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide (also known as CE-2072);

xvii. (benzyloxycarbonyl)-L-valyl-N-[1-(2-(3-(methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

xviii. (benzyloxycarbonyl)-L-valyl-N-[1-(2-(5-(methyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

xix. (benzyloxycarbonyl)-L-valyl-N-[1-(2-(5-(3-trifluoromethylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

xx. (benzyloxycarbonyl)-L-valyl-N-[1-(2-(5-(4-dimethylaminobenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

xxi. (benzyloxycarbonyl)-L-valyl-N-[1-(2-(5-(1-napthylenyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

xxii. (benzyloxycarbonyl)-L-valyl-[1-(3-(5-(3,4-methylenedioxybenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

xxiii. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-dimethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

xxiv. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-dimethoxybenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

xxv. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-ditrifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

xxvi. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-methylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

xxvii. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(biphenylmethine)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

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xxviii. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(4-phenylbenzyl)-1,2,4-
oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
xxix. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-phenylbenzyl)-1,2,4-
oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
       (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-phenoxybenzyl)-1,2,4-
XXX.
oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
xxxi. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(cyclohexylmethylene)-1,2,4-
oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
xxxii. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-trifluoromethyldimethylmethylene)-
1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
xxxiii. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(1-napthylmethylene)-1,2,4-
oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
xxxiv. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-pyridylmethyl)-1,2,4-
oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
xxxv. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-diphenylbenzyl)-1,2,4-
oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
xxxvi. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(4-dimethylaminobenzyl)-1,2,4-
oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
xxxvii. 2-(5-[(benzyloxycarbonyl)amino]-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-
pyrimidinyl]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-(S)-2-
methylpropyl]acetamide;
              2-(5-amino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(3-
xxxviii.
(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;
xxxix. 2-[5-[(benzyloxycarbonyl)amino]-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-
pyrimidinyl]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-(S)-2-
methylpropyl]acetamide;
       2-[5-amino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-(5-(3-
xl.
methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-methylpropyl]acetamide;
       (pyrrole-2-carbonyl)-N-(benzyl)glycyl-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-
xli.
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oxadiazolyl)carbonyl)-2-(S)-methylpropyl]amide;

- xlii. (pyrrole-2-carbonyl)-N-(benzyl)glycyl-N-[1-(3-(5-(3-trifluoromethylbenzyl)(1,2,4-oxadiazolyl)-(S)-methylpropyl]amide;
- xliii. (2S,5S)-5-amino-1,2,4,5,6,7-hexahydroazepino-[3,2,1]-indole-4-one-carbonyl-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-(R,S)-2-methylpropyl]amide;
- xliv. BTD-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]amide;
- xlv. (R,S)-3-amino-2-oxo-5-phenyl-1,4-benzodiazepine-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;
- xlvi. (benzyloxycarbonyl)-L-valyl-2-L-(2,3-dihydro-1H-indole)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]amide;
- xlvii. (benzyloxycarbonyl)-L-valyl-2-L-(2,3-dihydro-1H-indole)-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]amide; xlviii. acetyl-2-L-(2,3-dihydro-1H-indole)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]amide;
- xlix. 3-(S)-(benzyloxycarbonyl)amino)-ε-lactam-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;
- 1. 3-(S)-(amino)-ε-lactam-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide trifluoroacetic acid salt;
- li. 3-(S)-[(4-morpholinocarbonyl-butanoyl)amino]-ε-lactam-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(R,S)-methylpropyl]acetamide;
- lii. 6-[4-fluorophenyl]-ε-lactam-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;
- liii. 2-(2-(R,S)- phenyl-4-oxothiazolidin-3-yl]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;
- liv. 2-(2-(R,S)-phenyl-4-oxothiazolidin-3-yl]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl(hydroxymethyl)-2-(S)-methylpropyl]acetamide;
- lv. 2-(2-(R,S)-benzyl-4-oxothiazolidin-3-yl]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;
- lvi. 2-(2-(R,S)-benzyl-4-oxothiazolidin-3-yloxide]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(R,S,)-methylpropyl]acetamide;

lvii. (1-benzoyl-3,8-quinazolinedione)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;

lviii. (1-benzoyl-3,6-piperazinedione)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;

lix. (1-phenyl-3,6-piperazinedione)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;

lx. (1-phenyl-3,6-piperazinedione)-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)]-2-(S)-methylpropyl]acetamide;

lxi. 3-[(benzyloxycarbonyl)amino]-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;

lxii. 3-[(benzyloxycarbonyl)amino]-7-piperidinyl-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;

lxiii. 3-(carbomethoxy-quinolin-2-one-N-[1-(2-(5-(3-methybenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;

lxiv. 3-(amino-quinolin-2-one)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;

lxv. 3-[(4-morpholino)aceto]amino-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;

lxvi. 3,4-dihydro-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;

lxvii. 1-acetyl-3-(4-fluorobenzylidene)piperazine-2,5-dione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;

lxviii. 1-acetyl-3-(4-dimethylaminobenzylidene)piperazine-2,5-dione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;

lxix. 1-acetyl-3-(4-carbomethoxybenzylidene)piperazine-2,5-dione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;

lxx. 1-acetyl-3-[(4-pyridyl)methylene]piperazine-2,5-dione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;

lxxi. 4-[1-benzyl-3-(R)-benzyl-piperazine-2,5-dione]-N-[1-(2-[5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;

lxxii. 4-[1-benzyl-3-(S)-benzylpiperazine-2,5-dione]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;

lxxiii. 4-[1-benzyl-3(R)-benzylpiperazine-2,5-dione]-N-[1-(3-(5-(3-

trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;

lxxiv. 4-[1-benzyl-3-(S)-benzylpiperazine-2,5-dione]-N-[1-(3-(5-(3-

trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;

lxxv. 4-[1-benzyl-3-(S)-benzylpiperazine-2,5-dione]-N-[1-(3-(5-(2-

dimethylaminoethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;

lxxvi. 4-[1-methyl-3-(R,S)-phenylpiperazine-2,5-dione]-N-[1-(3-(5-(3-

trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;

lxxvii. 4-[methyl-3-(R,S)-phenylpiperazine-2,5-dione]-N-[1-(2-(5-(3-methylbenzyl)-

1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;

lxxviii. 4-[1-(4-morpholinoethyl)-3-(R)-benzylpiperazine-2,5-dione]-N-[1-(2-(5-(3-

methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;

lxxix. 5-(R,S)-phenyl-2,4-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-

oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;

lxxx. 5-(R)-benzyl-2,4-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-

oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;

lxxxi. 5-(S)-benzyl-2,4-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-

oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;

lxxxii. 5-(S)-benzyl-2,4-imidazolidinedione-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-

oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;

lxxxiii. 5-(R)-benzyl-2,4-imidazolidinedione-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-

oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;

lxxxiv. 1-benzyl-4-(R)-benzyl-2,5-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-

1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;

lxxxv. 1-benzyl-4-(R)-benzyl-2,5-imidazolidinedione-N-[1-(3-(5-(3-

 $trifluoromethylbenzyl) \hbox{-} 1, \hbox{2,4-} oxadiazolyl) \hbox{carbonyl}) \hbox{-} 2 \hbox{-} (S) \hbox{-} methylpropyl] acetamide;$ 

pharmaceutically acceptable salts thereof;

and combinations thereof.

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L. SHAPIRO

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9. (Withdrawn and Currently Amended) The method of Claim 8, in which the effective amount is at least 0.001 and no greater than 70 g/kg body weight.

- 10. (Original) The method of Claim 1, in which the subject is a human.
- 11. (Canceled)
- 12. (Original) The method of Claim 1, in which the therapeutically effective amount is sufficient to provide at least 10 pM and no greater than 2 mM of the inhibitor in the biological fluid of the subject.
  - 13. (Original) The method of Claim 12, in which the biological fluid is blood.
- 14. (Previously Amended) The method of Claim 1, in which the therapeutically effective amount is sufficient to provide at least .5  $\mu$ M and no greater than 2000  $\mu$ M in the biological fluid of the subject.
- 15. (Original) The method of Claim 1, in which the administering is parenterally, orally, vaginally, rectally, nasally, buccally, intravenously, intramuscularly, subcutaneously, intrathecally, epidurally, transdermally, intracerebroventricularly, by osmotic pump, or combinations thereof.
- 16. (Original) The method of Claim 1, in which the therapeutically effective amount is administered at least once daily and no more than once hourly.
- 17. (Original) The method of Claim 2, in which the monitoring is performed on a biopsy from the subject.

## 18.-22. (Canceled)

- 23. (Withdrawn) The method of Claim 25, in which the serine protease inhibitor is derivatized by esterification, acetylation, or amidation, and wherein the derivatized serine protease inhibitor retains the inhibitory activity.
- 24. (Withdrawn) The method of Claim 25, wherein the at least one cell is a cell of a subject, and wherein the amount is sufficient to bring the concentration of serine protease inhibitor in the subject's blood to at least .5  $\mu$ M and no greater than 200  $\mu$ M.
- 25. (Withdrawn) A method of inhibiting apoptosis, comprising providing a serine protease inhibitor to at least one cell and measuring a decrease in apoptosis, wherein the serine protease inhibitor is an oxidation-resistant or free radical-resistant variant of  $\alpha_1$ -antitrypsin; or:
  - i. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
  - ii. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(2-phenylethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
  - iii. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(2-methoxybenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
  - iv. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(trifluoromethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
  - v. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(methyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)- methylpropyl]-L-prolinamide;
  - vi. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(difluoromethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
  - vii. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(benzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
  - viii. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-methoxybenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)- methylpropyl]-L-prolinamide;

- ix. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(2,6-difluorobenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- x. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(trans-styryl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xi. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(trans-4-trifluoromethylstyryl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xii. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(trans-4-methoxystyryl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xiii. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-thienylmethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xiv. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(phenyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xv. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-phenylpropyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide.
- xvi. (benzyloxycarbonyl)-L-valyl-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide (also known as CE-2072);
- xvii. (benzyloxycarbonyl)-L-valyl-N-[1-(2-(3-(methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xviii. (benzyloxycarbonyl)-L-valyl-N-[1-(2-(5-(methyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xix. (benzyloxycarbonyl)-L-valyl-N-[1-(2-(5-(3-trifluoromethylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xx. (benzyloxycarbonyl)-L-valyl-N-[1-(2-(5-(4-dimethylaminobenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xxi. (benzyloxycarbonyl)-L-valyl-N-[1-(2-(5-(1-napthylenyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xxii. (benzyloxycarbonyl)-L-valyl-[1-(3-(5-(3,4-methylenedioxybenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xxiii. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-dimethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

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(benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-dimethoxybenzyl)-1,2,4-
oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
       (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-ditrifluoromethylbenzyl)-1,2,4-
XXV.
oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
xxvi. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-methylbenzyl)-1,2,4-
oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
xxvii. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(biphenylmethine)-1,2,4-
oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
xxviii. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(4-phenylbenzyl)-1,2,4-
oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
      (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-phenylbenzyl)-1,2,4-
oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
       (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-phenoxybenzyl)-1,2,4-
XXX.
oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
xxxi. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(cyclohexylmethylene)-1,2,4-
oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
xxxii. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-trifluoromethyldimethylmethylene)-
1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
xxxiii. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(1-napthylmethylene)-1,2,4-
oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
xxxiv. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-pyridylmethyl)-1,2,4-
oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
xxxv. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-diphenylbenzyl)-1,2,4-
oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
xxxvi. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(4-dimethylaminobenzyl)-1,2,4-
oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
xxxvii. 2-(5-[(benzyloxycarbonyl)amino]-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-
pyrimidinyl]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-(S)-2-
methylpropyl]acetamide;
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xxxviii. 2-(5-amino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; xxxix. 2-[5-[(benzyloxycarbonyl)amino]-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-(S)-2-methylpropyl]acetamide;

- xl. 2-[5-amino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-methylpropyl]acetamide;
- xli. (pyrrole-2-carbonyl)-N-(benzyl)glycyl-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]amide;
- xlii. (pyrrole-2-carbonyl)-N-(benzyl)glycyl-N-[1-(3-(5-(3-trifluoromethylbenzyl)(1,2,4-oxadiazolyl)-(S)-methylpropyl]amide;
- xliii. (2S,5S)-5-amino-1,2,4,5,6,7-hexahydroazepino-[3,2,1]-indole-4-one-carbonyl-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-(R,S)-2-methylpropyl]amide;
- xliv. BTD-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]amide;
- xlv. (R,S)-3-amino-2-oxo-5-phenyl-1,4-benzodiazepine-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;
- xlvi. (benzyloxycarbonyl)-L-valyl-2-L-(2,3-dihydro-1H-indole)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]amide;
- xlvii. (benzyloxycarbonyl)-L-valyl-2-L-(2,3-dihydro-1H-indole)-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]amide; xlviii. acetyl-2-L-(2,3-dihydro-1H-indole)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-

oxadiazolyl)carbonyl)-2-(S)-methylpropyl]amide;

- xlix. 3-(S)-(benzyloxycarbonyl)amino)-\(\varepsilon\)-1.actam-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;
- 3-(S)-(amino)-ε-lactam-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl) 2-(S)-methylpropyl]acetamide trifluoroacetic acid salt;
- li. 3-(S)-[(4-morpholinocarbonyl-butanoyl)amino]-ε-lactam-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(R,S)-methylpropyl]acetamide;

- lii. 6-[4-fluorophenyl]-ε-lactam-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;
- liii. 2-(2-(R,S)- phenyl-4-oxothiazolidin-3-yl]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;
- liv. 2-(2-(R,S)-phenyl-4-oxothiazolidin-3-yl]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl(hydroxymethyl)-2-(S)-methylpropyl]acetamide;
- lv. 2-(2-(R,S)-benzyl-4-oxothiazolidin-3-yl]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;
- lvi. 2-(2-(R,S)-benzyl-4-oxothiazolidin-3-yloxide]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(R,S,)-methylpropyl]acetamide;
- lvii. (1-benzoyl-3,8-quinazolinedione)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;
- lviii. (1-benzoyl-3,6-piperazinedione)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;
- lix. (1-phenyl-3,6-piperazinedione)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;
- lx. (1-phenyl-3,6-piperazinedione)-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)]-2-(S)-methylpropyl]acetamide;
- lxi. 3-[(benzyloxycarbonyl)amino]-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;
- lxii. 3-[(benzyloxycarbonyl)amino]-7-piperidinyl-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;
- lxiii. 3-(carbomethoxy-quinolin-2-one-N-[1-(2-(5-(3-methybenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;
- lxiv. 3-(amino-quinolin-2-one)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;
- lxv. 3-[(4-morpholino)aceto]amino-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;
- lxvi. 3,4-dihydro-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;

lxvii. 1-acetyl-3-(4-fluorobenzylidene)piperazine-2,5-dione-N-[1-(2-(5-(3methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; lxviii. 1-acetyl-3-(4-dimethylaminobenzylidene)piperazine-2,5-dione-N-[1-(2-(5-(3methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; 1-acetyl-3-(4-carbomethoxybenzylidene)piperazine-2,5-dione-N-[1-(2-(5-(3lxix. methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; 1-acetyl-3-[(4-pyridyl)methylene]piperazine-2,5-dione-N-[1-(2-(5-(3lxx. methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; 4-[1-benzyl-3-(R)-benzyl-piperazine-2,5-dione]-N-[1-(2-[5-(3-methylbenzyl)lxxi. 1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; lxxii. 4-[1-benzyl-3-(S)-benzylpiperazine-2,5-dione]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; lxxiii. 4-[1-benzyl-3(R)-benzylpiperazine-2,5-dione]-N-[1-(3-(5-(3trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; lxxiv. 4-[1-benzyl-3-(S)-benzylpiperazine-2,5-dione]-N-[1-(3-(5-(3trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; lxxv. 4-[1-benzyl-3-(S)-benzylpiperazine-2,5-dione]-N-[1-(3-(5-(2dimethylaminoethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; lxxvi. 4-[1-methyl-3-(R,S)-phenylpiperazine-2,5-dione]-N-[1-(3-(5-(3trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; lxxvii. 4-[methyl-3-(R,S)-phenylpiperazine-2,5-dione]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; lxxviii. 4-[1-(4-morpholinoethyl)-3-(R)-benzylpiperazine-2,5-dione]-N-[1-(2-(5-(3methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; lxxix. 5-(R,S)-phenyl-2,4-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; lxxx. 5-(R)-benzyl-2,4-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; lxxxi. 5-(S)-benzyl-2,4-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4oxadiazolyl)carbonyl)-2-(S)-methylpropyllacetamide;

lxxxii. 5-(S)-benzyl-2,4-imidazolidinedione-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;

lxxxiii. 5-(R)-benzyl-2,4-imidazolidinedione-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;

lxxxiv. 1-benzyl-4-(R)-benzyl-2,5-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide;

lxxxv. 1-benzyl-4-(R)-benzyl-2,5-imidazolidinedione-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]acetamide; pharmaceutically acceptable salts thereof; or combinations thereof.

## 26.-29. (Canceled)

30. (Previously Presented) The method of Claim 1 wherein the serine protease inhibitor inhibits at least one of trypsin, cathepsin G, tryptase TL-2, factor Xa, elastase, or proteinase-3.